

**ALPRAZOLAM EXTENDED RELEASE- alprazolam tablet, extended release  
Preferred Pharmaceuticals Inc.**

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**ALPRAZOLAM EXTENDED-RELEASE TABLETS, USP**

C-IV

40-9181

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**Rx Only**

**WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS**

**Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see *Warnings, Drug Interactions*].**

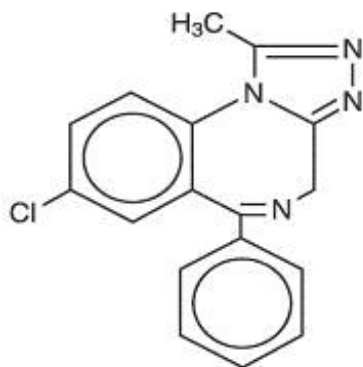
- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

**DESCRIPTION**

Alprazolam extended-release tablets, USP contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4*H*-s-triazolo [4,3- $\alpha$ ] [1,4] benzodiazepine. The molecular formula is C<sub>17</sub>H<sub>13</sub>ClN<sub>4</sub> which corresponds to a molecular weight of 308.76.

The structural formula is represented below:



Alprazolam, USP is a white crystalline powder, which is soluble in methanol or ethanol

but which has no appreciable solubility in water at physiological pH.

Each alprazolam extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are lactose monohydrate, hypromellose, and magnesium stearate. In addition, the 1 mg tablets also contain D&C yellow #10 aluminum lake. The 2 mg tablets also contain FD&C Yellow #6 aluminum lake, and the 3 mg tablets also contain D&C Yellow #10 aluminum lake, and FD&C Blue #2 aluminum lake.

Product meets USP Dissolution Test 2.

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

### **Pharmacokinetics**

#### **Absorption**

Following oral administration of alprazolam (immediate-release) tablets, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5 mg to 3.0 mg, peak levels of 8.0 ng/mL to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from alprazolam extended-release tablets is approximately 90%, and the relative bioavailability compared to alprazolam tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of alprazolam extended-release tablets are similar to that for alprazolam tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of alprazolam extended-release tablets. A high-fat meal given up to 2 hours before dosing with alprazolam extended-release tablets increased the mean  $C_{max}$  by about 25%. The effect of this meal on  $T_{max}$  depended on the timing of the meal, with a reduction in  $T_{max}$  by about 1/3 for subjects eating immediately before dosing and an increase in  $T_{max}$  by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ( $t_{1/2}$ ) were not affected by eating.

There were significant differences in absorption rate for the alprazolam extended-release

tablet, depending on the time of day administered, with the  $C_{max}$  increased by 30% and the  $T_{max}$  decreased by an hour following dosing at night, compared to morning dosing.

### Distribution

The apparent volume of distribution of alprazolam is similar for alprazolam extended-release tablets and alprazolam tablets. *In vitro*, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

### Metabolism

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam) were similar for alprazolam tablets and alprazolam extended-release tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam relative to unchanged alprazolam concentration after both alprazolam extended-release tablets and alprazolam tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and  $\alpha$ -hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxy-alprazolam and  $\alpha$ -hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

### Elimination

Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of alprazolam extended-release tablet ranges from 10.7 to 15.8 hours in healthy adults.

### Special Populations

While pharmacokinetic studies have not been performed in special populations with alprazolam extended-release tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of alprazolam tablets would not be expected to be different with the administration of alprazolam extended-release tablets.

Changes in the absorption, distribution, metabolism, and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function, and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0 to 26.9 hours,  $n=16$ ) compared to 11.0 hours (range: 6.3 to 15.8 hours,  $n=16$ ) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours,  $n=17$ ) as compared to between 6.3 and 26.9 hours (mean=11.4 hours,  $n=17$ ) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours,  $n=12$ ) as compared to between 6.3 and 15.8 hours (mean=10.6 hours,  $n=12$ ) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

*Race* - Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

*Pediatrics* - The pharmacokinetics of alprazolam after administration of the alprazolam extended-release tablet in pediatric patients have not been studied.

*Gender* - Gender has no effect on the pharmacokinetics of alprazolam.

*Cigarette Smoking* - Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

## **Drug-Drug Interactions**

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied *in vivo*, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed *in vivo*. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from  $0.90 \pm 0.21$  mL/min/kg to  $2.13 \pm 0.54$  mL/min/kg and the elimination  $t_{1/2}$  was shortened (from  $17.1 \pm 4.9$  to  $7.7 \pm 1.7$  h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS, Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1,000 mg/day to 1,200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

## **CLINICAL EFFICACY TRIALS**

The efficacy of alprazolam extended-release tablets in the treatment of panic disorder was established in two 6-week, placebo-controlled studies of alprazolam extended-release in patients with panic disorder.

In two 6-week, flexible-dose, placebo-controlled studies in patients meeting DSM-III criteria for panic disorder, patients were treated with alprazolam extended-release in a dose range of 1 mg/day to 10 mg/day, on a once-a-day basis. The effectiveness of alprazolam extended-release was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were seven primary efficacy measures in these studies, and alprazolam extended-release was superior to placebo on all seven outcomes in both studies. The mean dose of alprazolam extended-release at the last

treatment visit was 4.2 mg/day in the first study and 4.6 mg/day in the second.

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of alprazolam extended-release in patients with panic disorder, involving fixed alprazolam extended-release doses of 4 mg/day and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of alprazolam extended-release.

The longer-term efficacy of alprazolam extended-release in panic disorder has not been systematically evaluated.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

## **INDICATIONS AND USAGE**

Alprazolam extended-release tablets, USP are indicated for the treatment of panic disorder, with or without agoraphobia.

This claim is supported on the basis of two positive studies with alprazolam extended-release conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL EFFICACY TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of alprazolam extended-release has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

## **CONTRAINDICATIONS**

Alprazolam extended-release tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines.

Alprazolam extended-release is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS, Drug Interactions).

## **WARNINGS**

### **Risks from Concomitant Use with Opioids**

Concomitant use of benzodiazepines, including alprazolam extended-release, and opioids may result in profound sedation, respiratory depression, coma, and death.

Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe alprazolam extended-release concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of alprazolam extended-release than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking alprazolam extended-release, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when alprazolam extended-release is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **Drug Interactions**).

### **Dependence and Withdrawal Reactions, Including Seizures**

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at doses of less than or equal to 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of alprazolam tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received alprazolam extended-release tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received alprazolam tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to alprazolam tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety

and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71% to 93% of patients treated with alprazolam tablets tapered completely off therapy compared to 89% to 96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with alprazolam tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with alprazolam extended-release tablets. In two cases, the patients had completed 6 weeks of treatment with alprazolam extended-release 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued alprazolam extended-release, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with alprazolam extended-release 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of alprazolam tablets, the immediate-release form of alprazolam. Seizures attributable to alprazolam were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of alprazolam greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 mg to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from alprazolam. The risk of seizure seems to be greatest 24 to 72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

### **Status Epilepticus**

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of alprazolam tablets. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

### **Interdose Symptoms**

Early morning anxiety and emergence of anxiety symptoms between doses of alprazolam tablets have been reported in patients with panic disorder taking prescribed maintenance doses. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound, or withdrawal symptoms over the entire course of the interdosing interval.

## **Risk of Dose Reduction**

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (e.g., the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of alprazolam extended-release should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

## **CNS Depression and Impaired Performance**

Because of its CNS depressant effects, patients receiving alprazolam extended-release tablets should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with alprazolam extended-release tablets.

## **Risk of Fetal Harm**

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

## **Alprazolam Interaction with Drugs That Inhibit Metabolism Via Cytochrome P450 3A**

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

### **Potent CYP3A Inhibitors**

*Azole antifungal agents* - Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended



(see CONTRAINDICATIONS).

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

*Nefazodone* - Coadministration of nefazodone increased alprazolam concentration two-fold.

*Fluvoxamine* - Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

*Cimetidine* - Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

### **Other Drugs Possibly Affecting Alprazolam Metabolism**

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the **PRECAUTIONS** section (see PRECAUTIONS, Drug Interactions).

## **PRECAUTIONS**

### **General**

#### **Suicide**

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

#### **Mania**

Episodes of hypomania and mania have been reported in association with the use of alprazolam tablets in patients with depression.

#### **Uricosuric Effect**

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

#### **Use in Patients with Concomitant Illness**

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients (see DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic, or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with alprazolam tablets. A decreased systemic alprazolam elimination rate (e.g., increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving alprazolam tablets

(see CLINICAL PHARMACOLOGY).

## Information for Patients

To assure safe and effective use of alprazolam extended-release, the physician should provide the patient with the following guidance.

1. Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when alprazolam extended-release is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider.
2. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined (see **Drug Interactions**).
3. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
4. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
5. Inform your physician if you are nursing.
6. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
7. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
8. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.
9. Some patients may find it very difficult to discontinue treatment with alprazolam extended-release due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

## Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

## Drug Interactions

### Use with Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA<sub>A</sub> sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

#### Use with Other CNS Depressants

If alprazolam extended-release tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

#### Use with Imipramine and Desipramine

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of alprazolam tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

#### Drugs that inhibit alprazolam metabolism via cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)

*Fluoxetine* - Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

*Propoxyphene* - Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

*Oral Contraceptives* - Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of *in vitro* studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an *in vivo* drug interaction study involving a single dose of alprazolam 1 mg and steady state doses of sertraline (50 mg/day to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from *in vitro* studies of benzodiazepines other

than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nifedipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

### **Drug/Laboratory Test Interactions**

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

### **Pregnancy**

#### **Teratogenic Effects**

*Pregnancy Category D:* (see WARNINGS section).

#### **Nonteratogenic Effects**

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

#### **Labor and Delivery**

Alprazolam has no established use in labor or delivery.

#### **Nursing Mothers**

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

#### **Pediatric Use**

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

## Geriatric Use

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with alprazolam extended-release tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.

### Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Alprazolam Extended-Release Tablets

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received alprazolam extended-release tablets in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the patients treated with alprazolam extended-release tablets at a rate at least twice that of placebo) are shown in the following table.

### Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials

System Organ Class/Adverse Event	Percentage of Patients Discontinuing Due to Adverse Events	
	Alprazolam Extended-Release (n=531)	Placebo (n=349)
<b>Nervous system disorders</b>		
Sedation	7.5	0.6
Somnolence	3.2	0.3

Dysarthria	2.1	0
Coordination abnormal	1.9	0.3
Memory impairment	1.5	0.3
<b>General disorders/administration site conditions</b>	1.7	0.6
Fatigue		
<b>Psychiatric disorders</b>		
Depression	2.5	1.2

#### Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with Alprazolam Extended-Release Tablets

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with alprazolam extended-release where the incidence in patients treated with alprazolam extended-release was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with alprazolam extended-release (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).

#### Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Alprazolam Extended-Release

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam Extended-Release (n=531)	Placebo (n=349)
<b>Nervous system disorders</b>		
Sedation	45.2	22.6
Somnolence	23.0	6.0
Memory impairment	15.4	6.9
Dysarthria	10.9	2.6
Coordination abnormal	9.4	0.9
Mental Impairment	7.2	5.7
Ataxia	7.2	3.2
Disturbance in attention	3.2	0.6

Balance impaired	3.2	0.6
Paresthesia	2.4	1.7
Dyskinesia	1.7	1.4
Hypoesthesia	1.3	0.3
Hypersomnia	1.3	0
<b>General disorders/administration site conditions</b>		
Fatigue	13.9	9.2
Lethargy	1.7	0.6
<b>Infections and infestations</b>		
Influenza	2.4	2.3
Upper respiratory tract infections	1.9	1.7
<b>Psychiatric disorders</b>		
Depression	12.1	9.2
Libido decreased	6.0	2.3
Disorientation	1.5	0
Confusion	1.5	0.9
Depressed mood	1.3	0.3
Anxiety	1.1	0.6
<b>Metabolism and nutrition disorders</b>		
Appetite decreased	7.3	7.2
Appetite increased	7.0	6.0
Anorexia	1.5	0
<b>Gastrointestinal disorders</b>		
Dry mouth	10.2	9.7
Constipation	8.1	4.3
Nausea	6.0	3.2
Pharyngolaryngeal pain	3.2	2.6
<b>Investigations</b>		
Weight increased	5.1	4.3
Weight decreased	4.3	3.7
<b>Injury, poisoning, and procedural complications</b>		
Road traffic accident	1.5	0
<b>Reproductive system and breast disorders</b>		
Dysmenorrhea	3.6	2.9
Sexual dysfunction	2.4	1.1
Premenstrual syndrome	1.7	0.6
<b>Musculoskeletal and connective tissue</b>		

**disorders**

Arthralgia	2.4	0.6
Myalgia	1.5	1.1
Pain in limb	1.1	0.3

**Vascular disorders**

Hot flushes	1.5	1.4
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**Respiratory, thoracic,  
and mediastinal disorders**

Dyspnea	1.5	0.3
Rhinitis allergic	1.1	0.6

**Skin and subcutaneous  
tissue disorders**

Pruritis	1.1	0.9
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**Other Adverse Events Observed During the Premarketing Evaluation of Alprazolam  
Extended-Release Tablets**

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with alprazolam extended-release. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with alprazolam extended-release, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

*Cardiac Disorders: Frequent:* palpitation; *Infrequent:* sinus tachycardia

*Ear and Labyrinth Disorders: Frequent:* Vertigo; *Infrequent:* tinnitus, ear pain

*Eye Disorders: Frequent:* blurred vision; *Infrequent:* mydriasis, photophobia

*Gastrointestinal Disorders: Frequent:* diarrhea, vomiting, dyspepsia, abdominal pain; *Infrequent:* dysphagia, salivary hypersecretion

*General Disorders and Administration Site Conditions: Frequent:* malaise, weakness, chest pains; *Infrequent:* fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

*Musculoskeletal and Connective Tissue Disorders: Frequent:* back pain, muscle cramps, muscle twitching

*Nervous System Disorders: Frequent:* headache, dizziness, tremor; *Infrequent:* amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor

*Psychiatric System Disorders: Frequent:* irritability, insomnia, nervousness, derealization,



libido increased, restlessness, agitation, depersonalization, nightmare; *Infrequent*: abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

*Renal and Urinary Disorders: Frequent*: difficulty in micturition; *Infrequent*: urinary frequency, urinary incontinence

*Respiratory, Thoracic, and Mediastinal Disorders: Frequent*: nasal congestion, hyperventilation; *Infrequent*: choking sensation, epistaxis, rhinorrhea

*Skin and Subcutaneous Tissue Disorders: Frequent*: sweating increased; *Infrequent*: clamminess, rash, urticaria

*Vascular Disorders: Infrequent*: hypotension

The categories of adverse events reported in the clinical development program for alprazolam tablets in the treatment of panic disorder differ somewhat from those reported for alprazolam extended-release tablets because the clinical trials with alprazolam tablets and alprazolam extended-release tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with alprazolam tablets were generally the same as those reported in the clinical trials with alprazolam extended-release tablets.

Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated with Alprazolam Extended-Release Tablets.

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with alprazolam extended-release where the incidence in patients treated with alprazolam extended-release was two times greater than the incidence in placebo-treated patients.

**Discontinuation-Emergent Symptoms: Incidence in Short-Term, Placebo-Controlled Trials with Alprazolam Extended-Release**

System Organ Class/Adverse Event	Percentage of Patients Reporting Adverse Event	
	Alprazolam Extended-Release (n=422)	Placebo (n=261)
<b>Nervous system disorders</b>		
Tremor	28.2	10.7
Headache	26.5	12.6
Hypoesthesia	7.8	2.3
Paresthesia	7.1	2.7
<b>Psychiatric disorders</b>		
Insomnia	24.2	9.6
Nervousness	21.8	8.8
Depression	10.9	5.0
Derealization	8.0	3.8

Anxiety	7.8	2.7
Depersonalization	5.7	1.9
<b>Gastrointestinal disorders</b>		
Diarrhea	12.1	3.1
<b>Respiratory, thoracic and mediastinal disorders</b>		
Hyperventilation	8.5	2.7
<b>Metabolism and nutrition disorders</b>		
Appetite decreased	9.5	3.8
<b>Musculoskeletal and connective tissue disorders</b>		
Muscle twitching	7.4	2.7
<b>Vascular disorders</b>		
Hot flushes	5.9	2.7

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There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking alprazolam extended-release tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam extended-release tablets be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

### **Post Introduction Reports**

Various adverse drug reactions have been reported in association with the use of alprazolam tablets since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal

relationship to the use of alprazolam tablets cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).

**To report SUSPECTED ADVERSE EVENTS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/> for voluntary reporting of adverse reactions.**

## **DRUG ABUSE AND DEPENDENCE**

### **Physical and Psychological Dependence**

Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including alprazolam. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long-term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of alprazolam sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (e.g., 0.75 mg/day to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including alprazolam. It is recommended that all patients on alprazolam who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including alprazolam. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in

tapering and discontinuing from alprazolam, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving alprazolam. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

## **Controlled Substance Class**

Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and alprazolam extended-release tablets have been assigned to Schedule IV.

## **OVERDOSAGE**

### **Clinical Experience**

Overdosage reports with alprazolam tablets are limited. Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

### **General Treatment of Overdose**

As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including **CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS** should be consulted prior to use.

## **DOSAGE AND ADMINISTRATION**

Alprazolam extended-release tablets may be administered once daily, preferably in the

morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 mg/day to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

### **Dosing in Special Populations**

In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of alprazolam extended-release is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

### **Dose Titration**

Treatment with alprazolam extended-release may be initiated with a dose of 0.5 mg to 1 mg once daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of alprazolam extended-release.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (i.e., a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

### **Dose Maintenance**

In controlled trials conducted to establish the efficacy of alprazolam extended-release tablets in panic disorder, doses in the range of 1 mg/day to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 mg/day to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to alprazolam extended-release is unknown. However, periodic reassessment is advised. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

### **Dose Reduction**

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.


In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every three days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

### **Switch from Alprazolam (Immediate-Release) Tablets to Alprazolam Extended-Release Tablets**

Patients who are currently being treated with divided doses of alprazolam (immediate-release) tablets, for example 3 to 4 times a day, may be switched to alprazolam extended-release tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

### **HOW SUPPLIED**

Alprazolam extended-release tablets, USP are available as follows:

1 mg — Each yellow, round tablet imprinted with  on one side and 84 on the other contains 1 mg of Alprazolam, USP. Tablets are supplied in bottles of 60 (NDC 0228-3084-06).

Bottles of 30 Tablets NDC 68788-6943-3

Bottles of 60 Tablets NDC 68788-6943-6

Bottles of 90 Tablets NDC 68788-6943-9

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

### **ANIMAL STUDIES**

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

Manufactured by:

Actavis Elizabeth LLC

Elizabeth, NJ 07207 USA

Distributed by:

Actavis Pharma, Inc.

Parsippany, NJ 07054 USA

## **MEDICATION GUIDE**

### **Alprazolam (al pra' zoe lam) Extended-Release Tablets, USP      C-IV**

#### **What is the most important information I should know about alprazolam extended-release tablets?**

- **Alprazolam extended-release tablets are a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- **Alprazolam extended-release tablets can make you sleepy or dizzy, and can slow your thinking and motor skills.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how alprazolam extended-release tablets affect you.
  - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking alprazolam extended-release tablets without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, alprazolam extended-release tablets may make your sleepiness or dizziness much worse.
- Do not take more alprazolam extended-release tablets than prescribed.

#### **What are alprazolam extended-release tablets?**

- Alprazolam extended-release tablets are a prescription medicine used to treat panic disorder, with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)
- **Alprazolam extended-release tablets are a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep alprazolam extended-release tablets in a safe place to prevent misuse and abuse. Selling or giving away alprazolam extended-release tablets may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if alprazolam extended-release tablets are safe and effective in children.
- Elderly patients are especially susceptible to dose related adverse effects when taking alprazolam extended-release tablets.
- It is not known if alprazolam extended-release tablets are safe and effective for use longer than 8 weeks.

#### **Do not take alprazolam extended-release tablets if:**

- you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in alprazolam extended-release tablets. See the end of this Medication Guide for a

complete list of ingredients in alprazolam extended-release tablets.

- you are taking antifungal medicines including ketoconazole and itraconazole

**Before you take alprazolam extended-release tablets, tell your healthcare provider about all of your medical conditions, including if you:**

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have lung disease or breathing problems
- are pregnant or plan to become pregnant. Alprazolam extended-release tablets may harm your unborn baby. You and your healthcare provider should decide if you should take alprazolam extended-release tablets while you are pregnant.
- are breastfeeding or plan to breastfeed. Alprazolam passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take alprazolam extended-release tablets. You should not breastfeed while taking alprazolam extended-release tablets.

**Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**

Taking alprazolam extended-release tablets with certain other medicines can cause side effects or affect how well alprazolam extended-release tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

**How should I take alprazolam extended-release tablets?**

- **See “What is the most important information I should know about alprazolam extended-release tablets?”**
- Take alprazolam extended-release tablets exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how many alprazolam extended-release tablets to take and when to take it.
- Swallow alprazolam extended-release tablets whole. Do not crush, chew or break alprazolam extended-release tablets.
- If you take too many alprazolam extended-release tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

**What should I avoid while taking alprazolam extended-release tablets?**

- Alprazolam extended-release tablets can cause you to be drowsy. Do not drive a car or operate heavy machinery until you know how alprazolam extended-release tablets affect you.
- You should not drink alcohol while taking alprazolam extended-release tablets. Drinking alcohol can increase your chances of having serious side effects.

**What are the possible side effects of alprazolam extended-release tablets?**

**Alprazolam extended-release tablets may cause serious side effects, including:**

- **See “What is the most important information I should know about alprazolam extended-release tablets?”**
- **Abuse and dependence.** Taking alprazolam extended-release tablets can cause physical and psychological dependence. Physical and psychological dependence is



not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.

- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking alprazolam extended-release tablets suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping alprazolam extended-release tablets to avoid withdrawal symptoms.
- **Seizures.** Stopping alprazolam extended-release tablets can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** Alprazolam extended-release tablets may cause an increase in activity and talking (hypomania and mania) in people who have depression.

**The most common side effects of alprazolam extended-release tablets include:**

- sedation
- difficult or unclear ability to talk
- problems with coordination
- tiredness
- drowsiness
- depression
- memory problems

These are not all the possible side effects of alprazolam extended-release tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store alprazolam extended-release tablets?**

- Store alprazolam extended-release tablets between 59°F to 86°F ( 15°C to 30°C)
- **Keep alprazolam extended-release tablets and all medicines out of the reach of children.**

**General information about the safe and effective use of alprazolam extended-release tablets.**

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use alprazolam extended-release tablets for a condition for which it was not prescribed.
- Do not give alprazolam extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.
- You can ask your pharmacist or healthcare provider for information about alprazolam extended-release tablets that is written for health professionals. For more information call Actavis at 1-800-432-8534.

**What are the ingredients in alprazolam extended-release tablets?**

**Active ingredient:** alprazolam, USP

**Inactive ingredients:** lactose monohydrate, hypromellose, and magnesium stearate. In addition, the 1 mg tablets also contain D&C yellow #10 aluminum lake. The 2 mg tablets also contain FD&C Yellow #6 aluminum lake, and the 3 mg tablets also contain

D&C Yellow #10 aluminum lake, and FD&C Blue #2 aluminum lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Actavis Elizabeth LLC

Elizabeth, NJ 07207 USA

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## PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 68788-6943

CIV

Alprazolam Extended-Release Tablets, USP

1 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

Actavis

**Repackaged By: Preferred Pharmaceuticals Inc**

Rx Only

<b>Alprazolam Extended-Release Tablets 1mg (CIV)</b> Generic for Xanax Each extended-release tablet contains: Alprazolam, USP .. 1mg Pkg Size: Exp Date: Lot#: _____ Batch#: _____ Ins: _____ Mfg: Actavis Elizabeth LLC; Elizabeth, NJ Prod#: _____ Warning Store at 25°C (77°F); excursions permitted to 15° to 30° (59° to 86°F) See USP Controlled Room Temperature. Keep this and all medication out of the reach of children. Keep container tightly closed. Rx Only. Tablet is round, yellow, unprinted with R/ 84	 <b>Directions English</b> Take _____ Tablet(s) _____ time(s) a day	 <b>Instrucciones Espanol:</b> Cada _____ Tableta(s) _____ vece(s) al dia	CAUTION: Federal law PROHIBITS transfer of this drug to any person other than the patient for whom it was prescribed	Alprazolam Extended-Release Tablets 1mg (CIV) Qty: Ins: _____ Lot#: Bat#: _____ Prod# (NDC): _____ Alprazolam Extended-Release Tablets 1mg (CIV) Qty: Ins: _____ Lot#: Bat#: _____ Prod# (NDC): _____ Alprazolam Extended-Release Tablets 1mg (CIV) Qty: Ins: _____ Lot#: Bat#: _____ Prod# (NDC): _____ Alprazolam Extended-Release Tablets 1mg (CIV) Qty: Ins: _____ Lot#: Bat#: _____ Prod# (NDC): _____	Log Chart Billing Patient
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## ALPRAZOLAM EXTENDED RELEASE

alprazolam tablet, extended release

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68788- 6943(NDC:0228-3084)
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CIV

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
<b>ALPRAZOLAM</b> (UNII: YU55MQ3IZY) (ALPRAZOLAM - UNII:YU55MQ3IZY)	ALPRAZOLAM	1 mg

### Inactive Ingredients

<b>Ingredient Name</b>	<b>Strength</b>
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>HYPROMELLOSE, UNSPECIFIED</b> (UNII: 3NXW29V3WO)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I3O)	
<b>D&amp;C YELLOW NO. 10</b> (UNII: 35SW5USQ3G)	

### Product Characteristics

<b>Color</b>	YELLOW	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	10mm
<b>Flavor</b>		<b>Imprint Code</b>	R;84
<b>Contains</b>			

### Packaging

#	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:68788-6943-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2017	
2	NDC:68788-6943-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2017	
3	NDC:68788-6943-9	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/14/2017	

### Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
ANDA	ANDA078056	04/14/2017	

**Labeler** - Preferred Pharmaceuticals Inc. (791119022)

**Registrant** - Preferred Pharmaceuticals Inc. (791119022)

**Establishment**

<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-6943)

Revised: 2/2021

Preferred Pharmaceuticals Inc.